III. REMARKS

Claim Status

Claims 1-2, 5-7, 9-11 and 16-24 are active in the application. Claims 1, 9 and 19-21 have been amended. Claims 23-24 are new.

Summary of Applicant's Invention

Applicant's claims cover a oligonucleotide which is capable of binding to a telomerase protein. The oligonucleotide according to the invention is capable of binding to the telomerase simultaneously on two sites. It can bind to the template region of telomerase RNA and at the same time it is able of binding to the telomerase protein.

This dual binding is a very important feature of the invention. The dual binding is the reason why the oligonucleotide according to the invention is enormously effective, more than other inhibitors of telomerase in the state of the art.

At page 5, second fourth paragraph through page 6 first paragraph, applicant identifies the basis of the improved responses obtained by utilizing his novel oligomers.

> "According to the invention such chimeric oligonucleotides were prepared consisting of variously modified oligomeres optimized in view of the two targets and block, at the same time, the two enzyme binding sites of the telomeric DNA. These two differently modified parts of the oligonucleotide are linked together.

> They proved to be more efficient and selective than their individual components. In particular, chimeric oligonucleotides have proved to be successful, which are modified at the 5‘ end of the oligonucleotide by phosphorothioates, thus binding to the protein whereas being extended at the 3‘end, e.g. by phosphoamidates or, if necessary, via a linker by PNAs thus concerning telomerase RNA. In this way selectivity and efficiency of phosphorothioate-modified oligonucleotides is increased essentially. In addition, we found that a further, remarkable increase in efficiency may be reached if the 3‘ end of the chimeric oligonucleotides according to the invention is modified by such nucleosides which additionally inhibit the catalytic centre of the enzyme (e.g. 3‘azidodeoxyguanosine).”

Thus the novel oligonucleotides of claim 1 possess the novel and non-obvious capability of binding simultaneously to two sites of telomerase.

Applicants’ discovery of these specific oligonucleotides and the use of such phosphorothioate-modified oligomers as a part of the chimeric oligonucleotides which are linked to a second oligonucleotide, binding tightly to the template region of telomerase RNA.

Only through the linkage of both oligomers in which each part contributes to the inhibition of telomerase activity can the high level of inhibition be obtained. The synergistic effect is what makes applicants composition the most effective inhibitor of telomerase.

Claim Rejections - 35 USC § 112

Claims 9-11, 17, and 19-21 stand rejected under 35 U.S.C.

112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Instant claim 9 recites the oligonucleotide of claim 1, wherein the oligonucleotide is bound to telomerase.

Claims 10-11 and claim 17 recite the oligonucleotide of claim 1, wherein the oligonucleotide is bound to telomerase. The examiner considers the metes and bounds of these claims to be vague and indefinite since it is unclear to the examiner if the instant claims are merely drawn to the oligonucleotide of claim 1, wherein the oligonucleotide is capable of binding to a telomerase protein, or if these claims are drawn to an oligonucleotide, further comprising wherein the oligonucleotide is bound to telomerase in a complex, such that the claim is actually directed to the complex of the oligonucleotide bound to the telomerase protein, or further wherein the claim is drawn to a complex comprising the oligonucleotide claim 1 that is bound to an RNA component of the telomerase protein (see claim 17).

The examiner considers the metes and bounds of claims 10-11 to be vague and indefinite since it is unclear if the instant claims are drawn to merely the oligonucleotide of claim 1, or to a complex comprising an oligonucleotide, a telomerase, and a cell.

Applicant respectfully disagrees with the examiners analysis of the claims.

Claim 1 claims and oligonucleotide.

Claim 9 claims, *in haec verba*, the oligo bound to telomerase.

Claim 10, which is dependent upon claim 9 is limited by claim 9 and therefore claims the oligo bound to telomerase. Claim 11 is dependent upon claim 10 and is therefore bound by the limitations of claim 10 [and therefore indirectly of claim 9] and is also directed to the oligo bound to telomerase. Each of claims 10 and 11 is properly dependent because it contains further limitations.

Claim 17 is also dependent upon claim 9 and therefore is directed to the oligo bound to telomerase with the further limitation of the portion of the telomerase to which it is bound.

Claim 19-20 stand rejected to the extent that the nature of the claimed invention is unclear.

Applicant has amended claims 19 and 20 to recite that the protein site of claim 19 and the primer binding site recited in these claims are sites on the telomerase.

With regard to claim 21, the examiner states it is unclear if the claim is drawn to a single oligonucleotide of claim 1, or multiple since the claim recites "oligonucleotides of claim 1." Moreover, it is unclear if the instant claim is directed to the oligonucleotide only, or to a complex comprising said oligonucleotide and a cationic liposome.

Claim 21 has been amended to recite that it is a single oligo that is complexed.

Claim Rejections - 35 USC § 103

Claims 1-2, 5, 7, 9-11, 17-20, and 22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al. and Nielsen et al. (USP 5,539,082) in view of Norton et al. (1996) and Mata et al.

Applicant notes that in the immediately prior office action these same claims were rejected over Uhlmann et al. in view of Norton et al. (1996) and Mata et al.

The examiner's withdrawal of this rejection in favor of the new rejection is an implicit acknowledgement that applicant was persuasive in overcoming the prior rejection.

Thus the issue is whether the addition of Nielsen et al. (USP 5,539,082) adds disclosure that renders applicants claims obvious or whether Nielsen et al. is merely additive to the disclosure of the previously cited references in the withdrawn rejection or does not fill the missing element in the prior rejection.

In applicant's last response with regard to the combination of Uhlmann et al. in view of Norton et al. (1996) and Mata et al. applicant stated:

> "It is noted that the combination of references do not teach that n is at least 10 and not more than 20, and p is at least 3 and not more than 17."

Nielsen et al. does not cure this lacuna in the argument against patentability. Applicant therefore once again petitions the examiner to withdraw this ground for rejection.

Applicant further notes Nielsen et al. do not refer to oligonucleotides against telomerase RNA. Rather, Nielsen et al. present an effective modification of antisense ODN known as peptide nucleic acids, PNA, to increase the binding of the nucleic acid bases to complementary ssDNA or RNA sequences generally.

Applicants disclose using antisense ODN (with different modifications, including PNA) to reach the template site of telomerase RNA but, as described, applicants have linked them to second oligomers able to bind additionally to the telomerase protein.

Thus, two telomerase targets can be reached by applicants chimeric ODN: the primer binding site of the protein and the template region of RNA.

ODN which hit two targets of telomerase as do applicants chimeric ODN have never been described before and are not described by Nielsen et al.

For the examiner's ease in reconsideration of this ground for rejection applicant repeats, in the following, the points made in response to the last office action regarding this ground for rejection.

Uhlmann et al. teach the synthesis and properties of PNA and DNA chimeras of any desired sequence by an automated synthesizer and in one particular embodiment, disclose compounds of the following structure:

5'-GGGACCAtggcagcc-h where h is HN-$(CH_2)_6$-OH

which corresponds to nucleotides having oligomers on the 3' end of the structure comprising a terminal amino group having an acid labile protecting group.

However, as recognized by the examiner, Uhlmann et al. does not teach wherein n is at least 10 and not more than 20, and p is at least 3 and not more than 17. Moreover, Uhlmann et al. does not teach wherein this structure inhibits the activity of telomerase, or wherein the chimeric oligonucleotide structure comprises a terminal amino group.

Norton et al. is cited by the examiner as teaching the inhibition of human telomerase activity by peptide nucleic acids (PNAs). According to Norton et al. PNAs recognize the RNA component of human telomerase (hTR) and inhibit activity of the enzyme. Inhibition depends on targeting exact functional boundaries of the hTR template. Norton et al. also observed that phosphorothioate (PS) oligomers inhibit telomerase in a non-sequence selective fashion.

Additionally, Mata et al. is cited by the examiner as teaching that hexameric phosphorothioate oligomers function to inhibit telomerase activity and arrests growth of Burkitts lymphoma cells.

The examiner concludes that it would have been obvious to the ordinary skilled artisan to combine the teachings of the above-cited references in the design of the present invention and that one of ordinary skill in the art would have been motivated to make the oligomers of the present invention to comprise wherein n is at least 10 and not more than 20, and p is at least 3 and not more than 17, since Uhlmann et al. clearly

teach that chimeric PNA/DNA oligonucleotides or any sequence can be readily prepared.

The examiner also states that Norton et al. discloses the nucleotide structure of an oligomer 15 base pairs in length. Applicant has reviewed the Norton abstract cited by the examiner and respectfully, is unable to find reference in Norton to an oligomer 15 base pairs in length. Furthermore, even if the reference did have such disclosure, it would not lead one skilled in the art to an appreciation of the number of units of "n" and the number of units of "p" [now "z"] that are the crux of applicant's invention.

So all that is disclosed is a different composition that may by chemical manipulation be changed into the claimed compound, but without any understanding or motivation as to the benefit of the manipulation step.

As stated above Nielsen et al. do not cure the deficiencies in the examiner's argument.

Applicant believes a *prima facie* case has not been made by the examiner and therefore requests favorable reconsideration of this ground for rejection.

As an additional ground for positive reconsideration of claim 5, applicant notes that claim 5 requires that the nucleotides vary one from another and that is not disclosed in Nielsen et al., where adjacent nucleotides are repeated.

Claim Rejections - 35 USC § 102

Claims 1, 5, 9-11 and 19-22 stand rejected under 35

U.S.C. 102(b) as being anticipated by Iversen et al. ((WO 96/23508 Al).

It is noted that the prior art is applied to the extent that claims 9-11 and 19-21 are interpreted as reading on the oligonucleotide as recited in claim 1.

As stated by the examiner, Iversen et al. discloses oligonucleotides that for inhibiting proliferation of cancer cells comprising delivering an oligonucleotide comprising a nucleotide sequence which mimics a telomere repeat motif, wherein the oligonucleotide has a phosphorothioate backbone modification. The examiner points out that the phosphorothioate oligonucleotide having the following structure: 5'-d(TTAGGG)3-3' meets all the limitations of the instant claims to the extent that they read on oligonucleotides of formula III.

Applicants respectfully traverse this ground for rejection.

Iversen et al. demonstrates that it is not apparent that phosphoro-thioate-modified ODN bind outside the RNA to the primer binding site of telomerase protein. Iversen et al. claims “synthetic oligonucleotides which mimic telomeric sequences”. That phrase defines sequences complementary to the template region of the telomerase RNA (hTR, see the blue antisense oligomer in the enclosed Figure). These authors claim oligonucleotides which are very short and have the sequence TTAGGG. The backbone is modified by phosphorothioates.

This is readily distinguishable from applicants discovery (Nucleic Acids Res 1999, 27: 1152-1158) that the effects of phosphoro-thioate-modified oligonucleotides on telomerase are

sequence independent but length dependent and thus they cannot act as antisense oligonucleotides by binding to the telomerase RNA. However, as applicants have surprisingly discovered, they bind tightly to a protein site of telomerase, known as the primer binding site (see figure) with the consequence that they evidence a strong inhibition of telomerase activity.

Applicants confirmed this by finding that phosphorothioate backbones alone have the same inhibitory effect on telomerase activity although they carry no nucleic acid bases and are unable therefore to bind to the telomerase RNA (Oligonucleotides 2005,15: 255-268).

Most significantly, Iverson et al. is directed to a single short telomere motif, TTAGG. (Iversen et al. Abstract) As specifically noted by the examiner, this motif may be repeated several times (3 times in Iversen et al.'s Table 2 on page 21) but the sequence is unchanging and cannot therefore bind to two distinct regions of the telomere as is specifically required of applicants oligomers.

Conclusion

Based on the foregoing remarks it is believed that the claim is in condition for allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved. If any extension of time for this response is required, Applicants request that this be considered a petition therefore. Please charge any insufficiency of fees, or credit any excess to Deposit Account No. 14-1263.

Respectfully submitted,

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